

Vascular effects of diuretics in heart failure

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Diuretics have been the standard treatment for heart failure for several decades. The primary action is renal in promoting diuresis, but diuretics also alter vascular conductance and this may enhance their efficacy in heart failure.¹ The syndrome of chronic heart failure is associated with changes in vascular conductance peripherally and it is appropriate to summarise those changes before reviewing the vascular effects of diuretics.^{2,3} Patients with chronic heart failure, who are stabilised on treatment, are encouraged to exercise as part of modern management.⁴ Training improves exercise capacity. Exercise has been shown to alter vascular reactivity favourably both in normal people and patients with heart failure.^{5,6}

In chronic heart failure the resting cardiac output initially remains normal but is reduced during exercise. Also the normal physiological redistribution of blood flow to exercising muscles during exercise is decreased. This redistribution is achieved by muscular vasodilatation and splanchnic vasoconstriction. As the severity of heart failure increases both the resting and exercise cardiac output decrease and the redistribution is less, so that regional blood flow to exercising muscles and elsewhere is reduced.⁷

Vascular compliance is altered in heart failure. Both arterial and venoconstriction occur, and the muscular arteriolar bed becomes less able to vasodilate than normal. This is a

chronic change and has been likened to deconditioning.⁷ It is only seen with long-standing chronic heart failure as it takes several months to occur and resolves slowly when heart failure improves. When left ventricular dysfunction is acutely corrected by successful transplantation, the rapid return of normal haemodynamics does not change peripheral vascular conductance. Return to normal activity takes several months.⁸

How do diuretics alter vascular conductance? In heart failure there is increased salt and water retention in the arteriolar wall causing increased vascular stiffness and this is shown to be rapidly reversible after diuretic treatment (fig 1).⁹ This rapid change occurs in 24 hours and is associated with profuse diuresis. This is not related to any neurohumoral changes. Although diuresis continues over the next 24–48 hours there is no further change in the vascular compliance, and importantly it is still abnormal, which suggests the involvement of other factors as well as the mechanical changes caused by salt and water retention. The non-mechanical factor is related to deconditioning and increased neurohumoral activation. This component takes several weeks to return to normal. Thus diuretic treatment rapidly corrects the mechanical element of abnormal vascular compliance but the residual abnormality is aetiologically complex and requires considerable time to correct.

In chronic heart failure there is a relative decrease in venous capacitance due to venoconstriction. This can be found clinically with a rise in right atrial pressure during exercise in early heart failure without overt fluid retention.

In early studies intravenous frusemide was shown to alter venous capacitance (fig 2) as well as diuresis.¹⁰

Schuster and coauthors showed that in patients with acute pulmonary oedema, there were two separate responding groups—those who showed an acute diuresis and those who did not.¹¹ Interestingly, those with frusemide induced diuresis did not deplete their intravascular volume. Frusemide expanded the plasma volume independent of its diuretic action, which suggests that venous capacitance was altered lowering venous resistance. Capillary hydrostatic pressure decreased and colloidal osmotic pressure increased. An increase in the effective oncotic pressure gradient favours the reabsorption of extravascular or oedema fluid. Their studies show that the intravascular volume is replenished at a rate

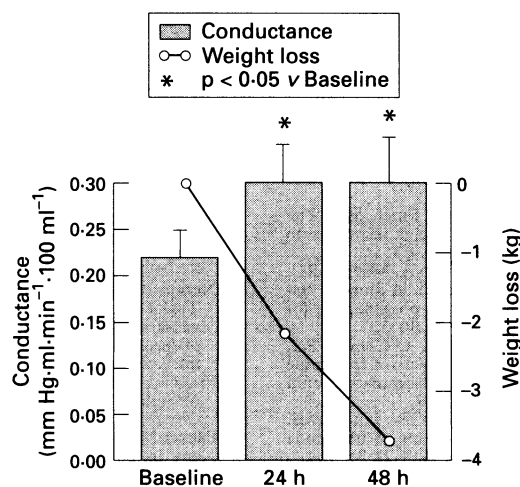
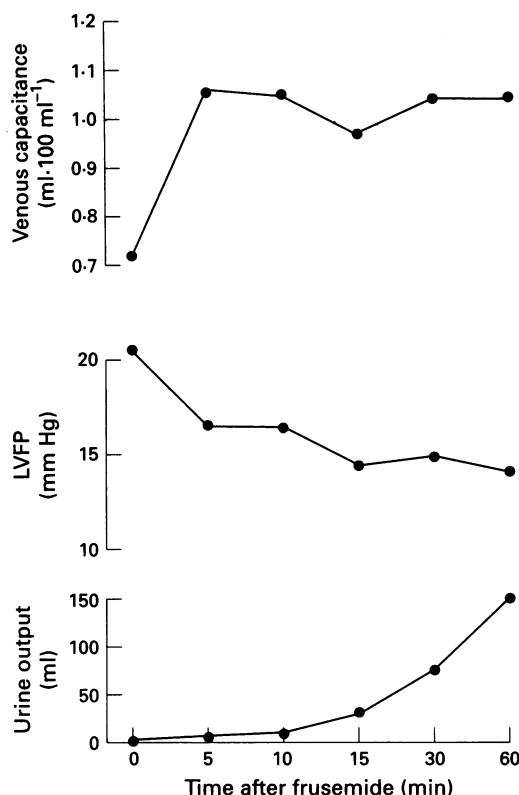


Figure 1 Relation between maximal forearm conductance calculated from the peak forearm reactive hyperaemic blood flow response and weight loss during diuretic treatment for congestive heart failure. Values are mean (SEM). Reproduced with permission.⁹

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Figure 2 Influence of intravenous frusemide on venous capacitance, left ventricular filling pressure (LVFP), and urine output in patients with left ventricular failure complicating acute myocardial infarction. Reproduced with permission.¹⁰



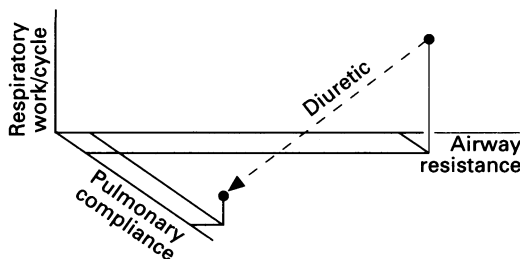
equal to or in excess of the volume removed by diuresis.

This elegant study shows that acutely the plasma volume is not decreased due to venodilatation. This was an acute study in patients with pulmonary oedema and may not be applicable to patients with chronic heart failure who have pulmonary oedema while on diuretic treatment.

Also, diuretic treatment alters pulmonary compliance in heart failure by pulmonary vasodilatation and reduction of pressure.¹² Lung water decreases two to four hours later. Air flow resistance is decreased and also the muscular work of breathing is decreased substantially (fig 3).

A hallmark of heart failure is the increase in systemic resistance due to vasoconstriction. This is caused by several factors including the activated neurohumoral system and deconditioning. Systemic resistance is known to decline during exercise in patients with heart failure as it does in normal people but the resistance at each stage of exercise is still higher than that in a normal person, again, emphasising the abnormal vascular reactivity that occurs in heart failure.¹³

Figure 3 Schematic representation of the effects of diuretics on pulmonary compliance, resistance to air flow, and respiratory work per cycle in congestive heart failure. Reproduced with permission.¹²



Differing acute vascular effects of frusemide and bumetanide

	Frusemide	Bumetanide
Forearm blood flow	Decreased	Nil
Mean arterial blood pressure	Decreased	Nil
Venous capacitance	Increased	Nil

The thiazide diuretics, including hydrochlorothiazide and indapamide, lower peripheral vascular resistance. This is independent of their renal diuretic effect.^{14 15} The mechanism seems to occur through the calcium or potassium activated channels and may vary with each drug. Neither drug seems to influence the eicosanoid system as indomethacin does not alter this effect. The loop diuretics have variable actions. Johnson and coauthors have shown that vascular effects differ between diuretics, and compared frusemide with bumetanide and showed that these two loop diuretics have differing vascular effects (table). The effects of frusemide on venous capacitance and peripheral blood flow occur usually when there is a salt retaining state and when frusemide causes acute renin release. These differences in vascular effects of diuretics have been shown, but it has yet to be shown if that is important in the treatment of heart failure. Nevertheless, it is important to assess in all new diuretics what their effect is on venous and systemic arterial capacitance in both the acute and chronic state of heart failure. Much of the data obtained on the effects of vascular capacitance with diuretics have been in patients with heart failure from acute myocardial infarction—that is, without longstanding chronic fluid retention. It may not be relevant to extrapolate these data to patients with chronic heart failure who are on chronic diuretic treatment. Francis *et al* measured the changes in acute haemodynamics in patients on chronic diuretic treatment given an acute dose of frusemide.¹⁶ This interestingly showed a depression of stroke volume and an increase in filling pressure in the first 20 minutes. Stroke volume increased and filling pressure decreased later at one hour after the diuretics. Venous capacitance was not measured during the study but arterial pressure and systemic vascular resistance increased during the early phase and may explain the haemodynamic deterioration. This suggests that acute intravenous frusemide, against a background of chronic treatment, may cause systemic vasoconstriction. Whether venous capacitance is relevant in the treatment of patients remains to be determined, but perhaps the action of diuretics in patients with chronic heart failure may be different from the changes in vascular compliance shown with acute diuretics in patients not on chronic treatment.

In conclusion diuretics alter vascular resistance in venous and arterial circuits. The acute and chronic effects differ. Different individual diuretics have different actions regardless of their class. The actions on the vascular system are complex and multifactor-

ial. The effects in acute and chronic heart failure may differ. Our knowledge of this is incomplete and it is uncertain if these effects are relevant in the overall treatment of heart failure.

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